REMARKS

After amendment, claims 1 and 4-27 remain pending, claim 3 being cancelled in order to advance prosecution of the instant application. Claim 2 was previously canceled. Applicants note that any subject matter cancelled herein is cancelled *without prejudice* and reserve the right for Applicants to refile claims containing such subject matter in any subsequent divisional or continuation application, if applicable. The amendment to the claims presented herein is supported by the originally filed application and claims. No new matter has been added by way of this amendment. It is respectfully submitted that the amended claims address the Examiner's concerns and the application is in condition for allowance.

Claims 1 and 4-17 are now pending after amendment. The claims have been amended so that they are now limited to the use of three or more compounds to give a better assessment of the status of *one* LSD, not comparing two of them. Given the tenor of the rejection in the first office action, the arguments presented in support of patentability of the previously pending claims and the nature of the recent office action of April 17, Applicants present the amended claims and arguments to address the Examiner's remaining concerns. In response to the Examiner's rejection and in order to obviate same, claim 3 is canceled and claim 17 is amended so that the claims no longer read on the use of two compounds.

The Prior Art Rejections

The Examiner has rejected the previously pending claims variously over 35 U.S.C. §§102 and 103 for the reasons which are presented in the April office action on pages 2-9. For the reasons which are presented below, Applicants respectfully submit that the amended claims are now novel and non-obvious over the cited references and should be passed to issue.

The Present Invention and Its Significance

Applicant's note that the aim of the present invention is not to better resolve the distinction between different types of LSD, but rather to better reflect the degree of severity of one LSD with the use of a profile of compounds. A side benefit of the present invention is that the approach may also better distinguish which type of LSD an individual has.

The claim amendments are presented to make clear that three compounds are used to assess the status of an individual for a single (one) LSD, and not to distinguish between different LSDs that an individual may suffer from. It is respectfully submitted that the amended claims distinguish over the cited prior art.

Response to the Examiner's Arguments Regarding the Teachings and Significance of Fujiwaki

> Regarding the prior art Fujiwaki, the Examiner states the following:
>
> "Fujiwaki teaches calculating an LSD index number using ratio of ceramide/sphingomyelin and ceramide/monohexosylceramide intensities; and comparing the LSD index number of the same with a standard (control sample) to provide an assessment of the LSD status of the individual (see page 171 left col. 5th paragraph). Therefore, Fujiwaki envisages calculating an index number using all three compound indicators (ceramide, sphingomyelin and monohexosylceramide)."

Applicant respectfully disagrees with the Examiner's statement. Fujiwaki does not teach calculating an index number derived from three different compound indicators. Nor is there even an oblique suggestion in Fujiwaki of calculating such an index number. In Fujiwaki, two ratios are presented for the individual affected by Faber disease (FD), each indicative of the level of ceramide, the two ratios each having a different internal control. They each measure the same thing, namely ceramide levels.

This is evidenced by the statement on page 171, in the left column of the 5th paragraph, where Fujwaki opens with the following statement:

"For the skin fibroblasts of the FD patient, as shown in Fig 1B, peaks for ceramides with different fatty acid carbon numbers, such as *m/z* 622 and 644, were observed, but were undetectable for control skin fibroblasts".

The above observation gleaned from Fujiwaki, clearly singles out ceramides as the compound that varies. That the ceramide varies is not all that surprising given that the defect in these individuals is known to lead to an accumulation of ceramides. (see, for example, the first sentence in the section of Fujiwaki headed "Discussion").

Fujiwaki then goes on to quantify the extent to which ceramides are elevated in the FD individual, tested by measuring the level of ceramide as against an internal control, that is, as against a compound that does not vary. Fujiwaki in this instance use two internal controls, namely sphingomyelin and monohexosylceramide. Unsurprisingly, Fujiwaki again comes to the conclusion that the peaks that are visible in Fig 1B are indeed reflected in the measured levels and states "These findings indicated the accumulation of ceramide in this patient."

The two different ratios used, namely ceramide/sphingomyelin and ceramide/monohexosylceramide are treated quite separately, which is not surprising given that they measure the same thing, in particular, the ceramide level, the only difference is that a different internal control is used. Thus, Applicants draw the attention of the Examiner to Figure 2A of Fujiwaki that shows a plot of the ceramide/sphingomyelin levels in the individual tested, and the separate plot of ceramide/monohexosylceramide in figure 2B. Applicants note that there is no plot of all three compounds, and there is simply no direction whatsoever in the text of the Fujiwaki document to use the three compounds in ***any*** calculation. The reason for this is very plain, because the two ratios measure the same thing, and there is no benefit to combining the two ratios into an index. In that regard, Applicants draw the attention of the examiner to the numerical value plotted in Fig 2 A and Fig 2 B for the FD individual - these are approximately the same. Combining the two results will not materially alter the value arrived at. There is

simply no point in the combination and that is the reason why Fujiwaki did not do so, why there is no suggestion in Fujiwaki to do so, and why the person of ordinary skill would not be motivated to do so.

In the first Office Action, the Examiner stated the following, which is reiterated in the present Office Action: that "each of these three compounds is indicative of the level of respective lipid containing storage associated compounds . . ." Applicants respectfully submit that the Examiner's statement is simply incorrect and misinterprets the teachings of Fujiwaki. Indeed, two of the compounds used in Fujiwaki (sphingomyeling and monohexosylceramide) are not indicative of the level, they merely act as internal controls. Thus, Fujiwaki cannot be seen as teaching the present invention.

> In the response to Applicants arguments on pages 9-10 of the April office action, the Examiner further states:
> "Fujiwaki shows that for Farbar disease patient, the ceramide/sphingomyelin and ceramide/monohexosylceramide intensity ratios are remarkably high . . , and for Gaucher disease patient, the ratio of monohexosylceramide/sphingomyelin intensity is high. That suggests that the use of two ratios is better than the use of one ratio for distinguishing Farbar disease from Gaucher disease."

Applicants respectfully submit that (without admitting the accuracy that statement is correct) they have canceled claim 3 and amended other claims that refer to the use of three or more compounds for differentiating between two different LSDs. In fact, Applicants submit that there is nothing in Fujiwaki that discloses the combination of the three compounds to produce an index figure to achieve a distinction between FD and GD, and further note that the compounds tested for in one of the ratios for FD is identical to those used to test GD.

In the following sections, Applicants address each of the Examiner's rejections.

The Rejection of Claims 1 and 3-9 As Being Anticipated by Fujiwaki

The Examiner has rejected originally filed claims 1 and 3-9 under 35 U.S.C. §102(b) as being anticipated by Fugiwaki, *Brain and Development*, 2002 ("Fujiwaki") for the reasons which are stated in the office action on pages 2-4. In response, Applicants respectfully submit that the presently pending claims are not anticipated by Fujiwaki.

Applicant refers to the remarks set forth above and the relationship of the disclosure in Fujiwaki to the newly presented claims. Applicants respectfully submit that claim 1 is novel because each of the elements presented in amended claim 1 is not found within the four corners of Fujiwaki, as explained above. The rejection of previously pending claim 3 is moot inasmuch as that claim has been cancelled.

The remaining rejected claims 4, 5, 6, 7, 8 and 9 are dependent on claim 1, which is novel over Fujiwaki for the reasons set out above. It is respectfully submitted that the presently pending claims are novel over the teachings of Fujiwaki.

The Obviousness Rejections under 35 U.S.C. §103

The Examiner has rejected 10-16, 23, 25, 17-22, 24, 26 and 27 variously over Fujiwaki, Whitfield, et al., *Molecular Genetics and Metabolism,* 2002 ("Whitfield"), Cable, et al., *Neurology,* 1982 ("Cable") and Aerts, et al., *Journal of Inherited Disease,* 1993, vol. 16, pages 288-291 ("Aerts") for the reasons which are set forth in the April 2009 office action on pages 3-9. For the reasons which are presented in detail hereinbelow, Applicants respectfully submit that the present invention is not disclosed by any one or more the references which have been cited against the present invention.

The Rejection of claims 10 - 16, 23 and 25 over Fujiwaki in view of Whitfield.

Claim 3 has been cancelled, and the dependency of claim 3 is therefore no longer extant. For the reasons set out above, Fujiwaki does not disclose calculating an index from at least three compounds to indicate that status of an LSD. Accordingly, the combination of Whitfield with Fujiwaki does not disclose or suggest the subject matter of these claims because neither of these citations disclose the combination of three compounds into an index figure for assessment of the severity of one LSD. As submitted in response to the first office action, Whitfield actually *teaches away* from using three indicator compounds to calculate an index.

Further, these claims are non-obvious for reasons set out in Applicants response to the First Office Action, the substance of which are referenced here.

The Rejection of claims 17 -22 over Fujiwaki in view of Cable.

As stated, claim 3 has been cancelled, and the dependency of claim 3 is therefore moot. For the reasons set out above, Fujiwaki does not disclose calculating an index from at least three compounds.

Cable does not disclose the use of three lipid associated markers to calculate an index, and discloses quantifying compounds as an adjunct to enzyme analysis. Thus, for the same reasons as for Whitfield, Cable teaches away from the use of three or more lipid associated compounds. There is no possible way that one of ordinary skill can combine Fujiwaki with Cable and produce the present invention.

Regarding the rejection of claim 22, the only manner in which these lipid associated markers have been utilized by the citations cited by the Examiner has been as *ratios*. None of the citations suggest combining a third marker. For reasons previously explained, both Whitfield and Cable each *teach away* from combining more than two markers. There is also no suggestion

to combine four lipid associated markers nor to calculate the combination set out in this claim. Claims 17-22 are clearly patentable over Fujiwaki in view of Cable.

The Rejection of claims 24 and 26 over Fujiwaki in view of Whitfield and further in view of Aerst

As discussed, claim 3 has been cancelled, and the dependency of claim 3 is therefore no longer relevant. For the reasons set forth above and as described in great detail, Fujiwaki does not disclose calculating an index from at least three compounds. Neither Whitfield nor Aerts disclose calculating an index from more than two compounds. Further, there is also absolutely no suggestion or motivation to combine four lipid associated markers or to calculate the combination set out in the claims of the present invention. Claims 24 and 26 are non-obvious over the cited prior art.

The Rejection of Claim 27 over Whitfield in view of Fujiwaki

As previously amended, claim 27 includes a limitation that the combination is formulated from "three or more . . indicators". For the reasons set out above, Fujiwaki does not disclose calculating an index from at least three compounds, Whitfield also does not teach calculating an index from at least three indicators, and otherwise teaches away from that approach. For the reasons set out above, Whitfield actually teaches *against* using three or more indicators, accordingly claim 27 is not disclosed.

For the reasons which have been presented in great detail hereinabove, it is respectfully submitted that the presently claimed invention now complies with the requirements of 35 U.S.C. Favorable consideration of this application is respectfully solicited.

For all of the above reasons, it is respectfully submitted that the present application is now in condition for allowance and such action is earnestly solicited. 1 claim has been cancelled (claim 3) and no new claims have been added to the present invention. No fee is therefore due

for the presentation of this amendment. A petition for an extension of time and a notice of appeal are enclosed as is the appropriate fee.

The Commissioner is authorized to charge any fee due or credit any overpayment to deposit account 04-0838.

Respectfully submitted,
COLEMAN SUDOL SAPONE, P.C.

By: _____
Henry D. Coleman
Reg. No. 32,559

714 Colorado Avenue
Bridgeport, Connecticut 06605-1601
(203) 366-3560
Dated: August 17, 2009

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450, on August 17, 2009.

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Henry D. Coleman